Appendix B

DRUG THERAPY

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DRUG THERAPY OF MIGRAINE

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MIGRAINE is an episodic headache that is unilateral or bilateral, pulsating in quality, moderate to severe in intensity, and exacerbated by physical activity. Associated symptoms include nausea or vomiting, photophobia, and phonophobia. The disorder is classified as migraine with aura (previously called classic migraine) and migraine without aura (previously called common migraine), according to the presence or absence, respectively, of premonitory neurologic symptoms.[1]

The pathophysiology of migraine is clearly related to disordered brain physiology, although neither the details nor the cause is known. The positive (stimulative) followed by negative (suppressive) neurologic symptoms of the aura and the slow spread of the neurologic deficit may be caused by spreading depression, a cortical neuronal event that can be elicited in animals by the application of potassium or glutamate to the brain.[2-4] In the past, the aura of migraine was attributed to cerebral vasospasm — a hypothesis for which there is still some support.[5] Head pain is attributed to activation of the trigeminovascular system.[6]

The goals of migraine treatment are amelioration of the symptoms of an acute attack and prevention of further attacks, either by behavioral or pharmacologic means.[7] The behavioral approach commonly involves regular sleep and meals and avoidance of initiating factors. Family- or work-related stress and emotional problems, which are frequently unavoidable, are best managed by various methods for coping with stress and by relaxation techniques.[8]

Determining the appropriate drug therapy for migraine is difficult. Distinguishing between migraine without aura and episodic tension headache is difficult and it is uncertain whether migraine with aura and migraine without aura are the same disorder as far as treatment is concerned. Interpretation of the results of therapeutic trials is complicated by a high rate of response to placebo, difficulties in measuring pain, and variability in the severity of attacks and associated symptoms. Many early trials were not conducted with the rigor that characterizes contemporary studies.[9]

SYMPTOMATIC TREATMENT OF ACUTE MIGRAINE

Analgesic Drugs

Aspirin, acetaminophen, propoxyphene, and codeine[10-13] are all superior to placebo in relieving the pain of migraine (Table 1). Effervescent formulations are more effective because they are absorbed more rapidly.[10] Because gastric stasis often accompanies migraine attacks, metoclopramide, a drug that increases gut motility and promotes gastric emptying, enhances the effectiveness of analgesic drugs.[10] Metoclopramide should not be used in adolescents, however, because it can cause dystonia, and it should be used sparingly in adults for the same reason. When nausea and vomiting are prominent, suppository preparations of both analgesic and antiemetic drugs can be given. The most commonly prescribed antiemetic drugs are perphenazine, prochlorperazine, and chlorpromazine. These drugs occasionally cause tardive dyskinesia, however, which may be irreversible, and patients should be informed of this risk before beginning treatment.

Two types of combined medications are often used in the treatment of migraine: isometheptene in combination with acetaminophen and dichloralphenazone (Midrin) and aspirin in combination with caffeine and butalbital (Fiorinal). Both combinations have addictive potential and a propensity to induce headache.[40] There is no evidence that these preparations are more effective than other analgesics. Fiorinal has been approved by the Food and Drug Administration (FDA) only for the treatment of tension headache. The FDA has classified Midrin as only possibly effective for migraine attacks. Nevertheless, these preparations may be effective in treating patients whose attacks do not respond to other analgesic drugs.

Major narcotic analgesic drugs, particularly meperidine, are used for emergency treatment of migraine attacks. The use of meperidine should be limited to patients who have severe infrequent attacks that do not respond to antimigraine preparations or patients in whom antimigraine drugs are contraindicated (e.g., those with peripheral vascular or coronary artery disease and pregnant women).

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs can be the first choice of treatment for patients with mild-to-moderately-severe migraine attacks. In a randomized, placebo-controlled, double-blind study, naproxen reduced the severity and duration of headache and photophobia in patients without aura.[15] In a randomized, parallel-group trial in which naproxen was compared with ergotamine,[16] naproxen was more effective in reducing the severity of headache, nausea, vomiting, and lightheadedness, but not in reducing the duration of the migraine attack. Naproxen does not always relieve vomiting.[17] In controlled trials, aspirin in oral doses of 500 mg also reduced pain in patients with acute migraine,[14] and intravenous administration of aspirin ameliorated acute migraine within 30 minutes in an uncontrolled trial.[41] Other effective nonsteroidal antiinflammatory drugs are listed in Table 1.[18-23] Metoclopramide used in combination with these drugs speeds their absorption and ameliorates nausea and vomiting, which a nonsteroidal antiinflammatory drug used alone may not reduce.

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Table 1. Drug Treatment of Migraine Attacks.*

Type of Drug	Recommended Dosage (mg)	References	Time to Peak Plasma Concentration (hr)	Important Side Effects
Analgesic				
Aspirin	500–650	Tfelt-Hansen and Olesen,[10] Hakkarainen et al.[12,14]	1	Dyspepsia, GI hemorrhage
Acetaminophen	500	Peatfield et al.[11]	1	Dyspepsia
Propoxyphene	65	Hakkarainen et al.[12,14]	1	Addiction
Codeine	60	Somerville[13]	1	Addiction, constipation
NSAID				
Naproxen sodium	750–825	Johnson et al.,[15] Pradalier et al.,[16] Nestvold et al.[17]	1–2	Dyspepsia, GI hemorrhage
Tolfenamic acid	200–400	Larsen et al.[18]	1–2	Same as for naproxen
Flufenamic acid	250–400	Carasso et al.[19]	1–2	Same as for naproxen
Mefenamic acid	500	Peatfield et al.[11]	1–2	Same as for naproxen
Flurbiprofen	300	Awidi[20]	1–2	Same as for naproxen
Diclofenac sodium	50–100	Karachalios et al.[21]	1–2	Same as for naproxen
Ibuprofen	200	Kloster et al.[22]	1–2	Same as for naproxen
Ketorolac (intramuscular)	30–60	Klapper and Stanton[23]	0.5–1	Same as for naproxen, plus asthma
5-HT agonist				
Ergotamine				
Oral	2–4	Hakkarainen et al.,[12,14] Selby and Lance,[24] Schmidt and Fanchamps,[25] Hakkarainen and Allonen[26]	1–2	Nausea, vomiting, abdominal pain, diarrhea, muscle cramps, limb paresthesia, vasoconstriction
Suppository	2	Selby and Lance[24]	0.5–2	
Sublingual	2–4	Selby and Lance[24]	?	
Dihydroergotamine				
Subcutaneous	0.75–1	Callaham and Raskin,[27] Saadah,[28] Belgrade et al.[29]	0.25–0.5	Same as for ergotamine but less severe
Sumatriptan				
Subcutaneous	6	Subcutaneous Sumatriptan International Study Group,[30] Sumatriptan Auto-Injector Study Group,[31] Cady et al.[32]	0.25	Flushing, heat, tingling, neck pain, chest heaviness, pressure, pain
Oral	100	Oral Sumatriptan International Multiple-Dose Study Group,[33] Anderson,[34] Multinational Oral Sumatriptan and Cafergot Comparative Study Group,[35] Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group[36]	1.5	
Dopamine antagonist				
Metoclopramide (intravenous)	10	Tek et al.[37]	<0.25	Dystonia
Chlorpromazine (intravenous)	0.1 mg/kg of body weight	Lane et al.[38]	<0.25	Tardive dyskinesia
Prochlorperazine (intravenous)	10	Jones et al.[39]	<0.25	Tardive dyskinesia

*GI denotes gastrointestinal, and NSAID nonsteroidal antiinflammatory drug.

Ketorolac, the first of these drugs available for parenteral administration in the United States, can be used for emergency treatment of severe migraine attacks complicated by vomiting, although the drug is less effective than other parenteral antimigraine preparations.[23] No studies have examined the relative efficacy of the various classes of nonsteroidal antiinflammatory drugs with respect to their antiinflammatory or analgesic properties. Furthermore, whether the inefficacy of one class suggests the inefficacy of another is not known, despite the customary practice of changing from one class to another if the first proves ineffective.

The proposed explanation for the effectiveness of the drugs that inhibit prostaglandin synthesis is that they prevent neurogenically mediated inflammation in the trigeminovascular system.[42] Prostaglandin-induced hyperalgesia can last for hours, although prostaglandins have a half-life of minutes.[43] Prostaglandins apparently activate secondary mechanisms that remain active long after the prostaglandins have been catabolized. This may explain why prostaglandin inhibitors are less effective when treatment of a migraine attack is delayed and why headache is often not completely relieved. Prostaglandin inhibitors may also interfere with serotonin neurotransmission and modulate vasoconstriction.[44]

Ergot Preparations

For many years, ergotamine tartrate was the drug of choice for treatment of moderate-to-severe migraine attacks. In controlled trials, ergotamine has proved to be effective in no more than 50 percent of patients when given orally, sublingually, rectally, or nasally.[24] The addition of caffeine to ergotamine enhances its absorption[25] and possibly its vasoconstrictive activity. Because absorption of ergotamine and related drugs is variable, they should be given by a route that is acceptable to the patient, and the doses should be increased to a single effective dose as early

as possible in subsequent attacks. Ergotamine is best absorbed rectally. Metoclopramide may improve the absorption of ergotamine administered orally.[26] An antiemetic drug (best given by means of a suppository) may be needed with ergotamine. Since it has vasoconstrictor actions and can cause ischemia, ergotamine is contraindicated in patients with coronary artery or peripheral vascular disease. The side effects are listed in Table 1.

Dihydroergotamine, which is available for parenteral use in the United States, is effective in treating migraine attacks, although it has not been studied in large numbers of patients. Up to 90 percent of attacks stopped when the drug was given intravenously in trials,[27,28] but up to 26 percent of patients required additional doses because of recurrent headache.[28] In these trials, dihydroergotamine was given in combination with a phenothiazine, which is also beneficial when used alone.[39] Dihydroergotamine is superior both to meperidine plus hydroxyzine and to butorphanol.[29] Patients can be instructed to give themselves dihydroergotamine subcutaneously. The drug is a vasoconstrictor and should therefore not be given to patients with vascular disease. The side effects of dihydroergotamine are similar to those of ergotamine.

Sumatriptan

Sumatriptan is a serotonin (5-hydroxytryptamine [5-HT])-receptor agonist that has recently been proved effective in treating migraine and is now available in the United States for that purpose. As of March 1992, a total of 48,452 attacks of migraine had been treated with sumatriptan in 10,502 patients.[45] At the recommended dose of 6 mg given subcutaneously or 100 mg given orally, peak plasma concentrations of sumatriptan are achieved at 10 minutes (72 μg per liter) and 1.5 hours (54 μg per liter), respectively.[46] The bioavailability is over 90 percent after subcutaneous administration but only 14 percent after oral administration. From 14 to 21 percent of sumatriptan in plasma is protein-bound. The drug is transformed in the liver to an inactive indoleacetic acid metabolite that is excreted predominantly in the urine, although oral administration increases fecal excretion. The elimination half-life of sumatriptan is approximately two hours.

Sumatriptan is effective when administered subcutaneously during an attack of migraine. In three trials, one of which involved self-administration of the drug, a subcutaneous dose of 6 mg resulted in improvement in 70 to 77 percent of patients within one hour after treatment and in 81 to 86 percent within two hours after treatment.[30-32] Nausea and vomiting were relieved in most patients within one to two hours after treatment, and the need for other analgesic medications was greatly reduced in the patients treated with sumatriptan, as compared with those receiving placebo (12 to 20 percent vs. 44 to 61 percent, respectively). A routine second subcutaneous injection of sumatriptan one hour after the first did not improve the outcome. Headache recurred in 38 to 46 percent of patients within 24 hours, probably because of the short half-life of the drug.

When sumatriptan was given orally in 100-mg doses, 75 percent of patients reported relief of headache and other symptoms within four hours.[33] Headache recurred, however, within 24 to 48 hours in up to 44 percent of patients, although it was treated effectively in up to 74 percent of patients by a second 100-mg dose.[34] Oral sumatriptan was more effective in relieving headache than either ergotamine plus caffeine or aspirin plus metoclopramide, but the rate of recurrence was higher with sumatriptan.[35,36] In relieving nausea and vomiting, sumatriptan was more effective than ergotamine and was as effective as aspirin with metoclopramide.

The side effects of subcutaneous and oral sumatriptan are generally similar. Most side effects are mild to moderate in intensity, are short-lived, resolve spontaneously, and do not change with repeated use of the drug. The most common side effects are reaction at the injection site after subcutaneous administration; sensations of flushing, heat, and tingling; and neck pain with stiffness (Table 1). Three to 5 percent of patients have chest tightness, heaviness, pressure, or pain. In some patients, the chest pressure or pain radiates to the left arm and hand, suggesting angina pectoris,[47] but electrocardiographic evidence of myocardial ischemia is rare. To date, with reports on over 3 million attacks treated with sumatriptan, only 4 patients have had myocardial ischemia due to coronary vasospasm, 1 of whom also had cardiac arrhythmia[48-50] (1 case on file with Glaxo, the manufacturer). All four patients had underlying cardiovascular disease. Myocardial infarction was reported in a 47-year-old woman with no history of coronary artery disease.[51] Sumatriptan does constrict coronary arteries,[52] but the effect is minor; 10 patients undergoing diagnostic coronary angiography had a 14 percent reduction in the diameter of the coronary arteries.[53] Extensive monitoring in 2500 patients and normal subjects given sumatriptan revealed no relation between chest symptoms and myocardial ischemia,[45] even though some patients had chest symptoms again when rechallenged with the drug.[54] The cause of the chest symptoms is uncertain, but in rare cases coronary vasospasm has undoubtedly occurred.

The first dose of sumatriptan should probably be given under medical supervision to those patients who are likely to have unrecognized coronary artery disease, such as postmenopausal women, men over 40 years of age, and patients with risk factors for coronary vascular disease. The drug is contraindicated in patients with a history of myocardial infarction, symptomatic ischemic heart disease, Prinzmetal's angina, or hypertension. Sumatriptan should not be used with ergotamine preparations or vasoconstrictor drugs in general, nor should it be used when methysergide has been prescribed for prevention of migraine, because methysergide also has vasoconstrictor properties. In view of the theoretical concern about the

"serotonin syndrome" (restlessness, myoclonus, hyperreflexia, diaphoresis, and tremors) and limited data on coadministration, some regulatory authorities have stipulated that sumatriptan not be given to patients receiving monoamine oxidase–inhibitor drugs, specific 5-HT–reuptake inhibitors, or lithium carbonate. Sumatriptan is not indicated for prophylaxis of migraine.

Mechanisms of Action of Sumatriptan and Ergotamine

Currently, four classes of 5-HT receptor are recognized: 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4.[55] Sumatriptan is a highly selective agonist of the D subtype of 5-HT_1 receptors located on peripheral trigeminal-nerve terminals that supply pain-sensitive vascular and meningeal structures. It has the same degree of affinity and selectivity for the subtype of 5-HT_1 receptors located on intracranial vessels, where it mediates contraction, particularly of large arteries. Local release of peptides from sensory axons (involving an axon reflex) of the trigeminal-nerve supply to certain extracranial arteries, meningeal tissues, dural arteries, and the dural sinuses may cause sensitivity to pain (neurogenic inflammation) and promote local vasodilatation during a migraine attack.[56] Calcitonin-gene–related peptide is released into jugular venous blood during a migraine attack,[57] and this release is blocked by sumatriptan.[58] Acting presynaptically, sumatriptan blocks the neuropeptide-mediated inflammatory response after trigeminal stimulation and may also block transmission in trigeminal neurons.[56] The direct vasoconstrictive action of sumatriptan may also alleviate headache.[55]

Ergotamine and dihydroergotamine have similar actions, and both have high affinity but less selectivity for 5-HT_1 receptors.[55,56] Dihydroergotamine is a potent venoconstrictor, and it also has arterial vasoconstrictor effects,[59] which may alleviate headache.

Dopamine Antagonists

Three dopamine-antagonist drugs have been used for the emergency treatment of severe, intractable migraine attacks. In one trial, migraine was relieved in 67 percent of patients given a 10-mg intravenous dose of metoclopramide, a nonphenothiazine central dopamine antagonist, as compared with 19 percent of those given placebo.[37] In other trials, chlorpromazine, given in three intravenous injections of 0.1 mg per kilogram of body weight 15 minutes apart, was more effective than meperidine in combination with dimenhydrinate,[38] and prochlorperazine, given in a dose of 10 mg intravenously, was superior to placebo.[39] All three drugs offer an alternative to narcotic analgesic drugs and to the more specific antimigraine drugs. Indeed, in a single-blind, randomized trial, chlorpromazine was superior to dihydroergotamine when each was given intravenously.[60] The side effects of the three drugs, in addition to dystonia and tardive dyskinesia (Table 1), are drowsiness, nausea, vomiting, dizziness, and hypotension, all of which are infrequent. The mechanism by which these dopamine-antagonist drugs relieve headache remains to be determined; adrenergic blockade, anti–5-HT activity, antiemetic action, and modulation of pain systems have all been hypothesized.[37-39,60]

Choice of Symptomatic Treatment

Since judgment may be impaired during prolonged, severe attacks of migraine, the patient may be uncertain about the type of drug used or the amount taken earlier. For this reason, family or friends should be instructed in the use of medications for acute migraine. A simple analgesic or nonsteroidal anti-inflammatory drug is appropriate for mild-to-moderate attacks, and ergotamine or sumatriptan for moderate-to-severe attacks. Prescription costs should be taken into account. Because the cost of sumatriptan is high, its use should be reserved for cases in which other medications have been ineffective or have had intolerable side effects. Attacks that are severe, prolonged, and unresponsive to self-administered medication may be treated in the clinic or emergency room. Patients with these types of attacks should be treated with dihydroergotamine given intravenously or intramuscularly or with sumatriptan given subcutaneously. If these treatments fail, metoclopramide, prochlorperazine, or chlorpromazine can be used. Acute attacks may be so frequent and the patient's pain so severe and continuous that hospitalization is required. In these cases, dihydroergotamine given intravenously for three to four days, discontinuation of all other drugs, and administration of intravenous fluids may prove effective.[61]

Prevention of Migraine

Preventive treatment should be considered only when attacks of migraine occur more than two or three times a month, the attacks are severe and limit normal activity, the patient is unable to cope with the attacks, symptomatic therapies have failed or had serious side effects, and attempts at nonpharmacologic prevention have failed. Several points should be considered before preventive therapy is initiated. Some form of contraception (preferably barrier rather than oral contraception, since the latter may trigger headaches) should be advised for women of childbearing age. Other medications, especially vasodilators, may also trigger headaches and should be discontinued, if possible. Patients who take large amounts of medications to treat headaches may not respond to preventive medication because the drugs compete for monoamine-receptor sites.[62] Therefore, the former medications should be discontinued. Drug costs should always be considered, because prolonged treatment may be required.

Each medication should be given for an adequate time to judge its effectiveness. For patients with frequent migraine, this period is usually two to three months. The lowest dose should be given at the outset and then increased in such a way that no more than three increments will be needed to achieve the maximal dose. Preventive medication is usually continued

for six months or longer and gradually withdrawn after the frequency of headaches diminishes.

5-HT–Influencing Drugs

The 5-HT–influencing drugs that are most effective for preventing migraine are methysergide and amitriptyline[63-65] (Table 2). Phenelzine had only a moderate effect in one trial.[67] There are two other drugs of this type: pizotyline and cyproheptadine. The former is not available in the United States, and the latter has never been studied in a controlled trial. Methysergide is more effective than amitriptyline[64] but is not used much in the United States because it can cause retroperitoneal, cardiac valvular, and pleural fibrosis. In other countries, however, the drug is used more widely and has proved to be safe if it is given in the recommended doses and if treatment is interrupted periodically. Methysergide is contraindicated in patients with vascular disease because of its vasoconstrictor action.

Amitriptyline is very useful for preventing migraine, especially in patients who also have depression or tension headaches, although its beneficial effect in migraine is independent of its antidepressant activity.[66] In a double-blind trial amitriptyline was superior to placebo.[65]

Methysergide and amitriptyline may prevent migraine by blocking 5-HT_2 receptors on cerebral vessels and central neurons.[93] Amitriptyline also suppresses neuronal activity in brain-stem raphe nuclei.[94]

Beta-Adrenergic Antagonists

Numerous clinical trials have shown that beta-adrenergic–antagonist drugs are effective in preventing migraine (Table 2).[68-75] They should be considered the treatment of choice for this purpose, especially in patients whose attacks of migraine are related to stress. These drugs, however, are effective in no more than 65 percent of patients. Their side effects, reported in up to 29 percent of patients in these trials, are listed in Table 2. Beta-adrenergic–antagonist drugs are contraindicated in patients with bronchospasm, congestive heart failure, cardiac arrhythmias, or a history of depression. No particular drug of this type is superior to the others, nor are long-acting preparations superior to standard preparations.

The mechanism of action of beta-adrenergic antagonists is not understood.[95] There is no correlation between the efficacy of these drugs and their entry into the central nervous system, membrane-stabilizing properties, ability to block 5-HT receptors, or beta-receptor selectivity. Beta-receptor antagonists with partial agonist activity are ineffective against migraine. Those that are effective increase peripheral vascular resistance, but it is difficult to explain their

Table 2. Drugs Used to Prevent Migraine.*

Type of Drug	Daily Oral Dosage (mg)	References	Effectiveness†	Important Side Effects
5-HT–Influencing				
Methysergide	2–8	Lance et al.,[63] Drummond[64]	++	Muscle cramps, insomnia, tissue fibrosis
Amitriptyline	10–150	Couch et al.[65,66]	++	Weight gain, drowsiness, dry mouth, blurred vision, cardiac arrhythmias, urinary retention, muscle cramps
Phenelzine	15–75	Anthony and Lance[67]	?	Weight gain, hypertensive crisis
β-Adrenergic antagonist				
Propranolol	40–320	Weber and Reinmuth,[68] Wideroe and Vigander[69]	++	Fatigue, nausea, depression, bradycardia, hypotension, bronchospasm
Propranolol (long-acting)	60–320	Kuritzky and Hering[70]	++	Weight gain, violent dreams, paresthesia
Metoprolol	200	Kangasniemi et al.[71]	++	Same as for propranolol
Atenolol	40–100	Stensrud and Sjaastad,[72] Johansson[73]	++	Same as for propranolol
Timolol	20	Hakkarainen and Kangasniemi[74]	+	Same as for propranolol
Nadolol	80–240	Ryan et al.[75]	++	Same as for propranolol
Calcium-channel blocker				
Nifedipine	30	Albers et al.,[76] McArthur et al.[77]	?, 0	Headache, tachycardia, depression
Nimodipine	120	Gelmers,[78] Havanka-Kanniainen et al.,[79] Meyer and Hardenberg,[80] Stewart et al.[81]	?	Headache, tachycardia, weight gain, constipation, depression
Verapamil	280–320	Solomon et al.,[82] Markley et al.,[83] Markley[84]	?	Headache, bradycardia, weight gain, constipation, depression
NSAID				
Ketoprofen	150	Stensrud and Sjaastad[85]	?	Dyspepsia, gastritis, GI bleeding, diarrhea
Tolfenamic acid	300	Mikkelsen and Falk[86]	?	Same as for ketoprofen
Mefenamic acid	500–1500	Johnson et al.[87]	+	Same as for ketoprofen
Naproxen sodium	1100	Welch et al.[88]	++	Same as for ketoprofen, plus fluid retention
Aspirin	1300	Masel et al.,[89] Buring et al.[90]	+	Dyspepsia, gastritis, GI bleeding
Miscellaneous				
Valproic acid	800–1000	Sorensen,[91] Hering and Kuritzky[92]	+	Hair loss, weight gain, hepatic dysfunction, neural-tube defect

*NSAID denotes nonsteroidal antiinflammatory drug, and GI gastrointestinal.

†For effectiveness, ++ denotes most effective, ? uncertain, + effective, and 0 ineffective.

beneficial effect on the basis of a peripheral vascular mechanism. Central effects on cortical and subcortical pathways are probably more important.[96,97]

Calcium-Channel–Blocking Drugs

Despite initial enthusiasm for the use of calcium-channel–blocking drugs to prevent migraine, their effect has been unimpressive. Nifedipine was beneficial in one clinical trial but not in another.[76,77] There have been several trials of nimodipine. In one, nimodipine resulted in a 66 percent reduction of a "weighted migraine index" (based on the frequency, duration, and severity of attacks), as compared with a 19 percent reduction for the placebo group.[78] Mild-to-moderate attacks were not taken into account, frequency was not reported, and a high dropout rate due to treatment failure was not included in the analysis. In another study, the number of patients was small, and the benefit of nimodipine as compared with placebo was an unimpressive reduction in the frequency and severity of attacks of 25 percent and 28 percent, respectively.[79] A third study, in which two doses of nimodipine were compared, had methodologic flaws, included patients with cluster headache, and used base-line comparisons for effectiveness.[80] A more recent controlled study claiming a benefit for nimodipine had similar flaws.[81] Verapamil has been evaluated in two crossover trials.[82,83] In each, the number of patients was small and the dropout rate was high, and neither trial provided substantial evidence of benefit, although both claimed it. Other, larger studies of verapamil[84] were not randomized or open in design and were poorly controlled, making the results unconvincing. Another drug of this type, flunarizine, has been used in Europe but is not available in the United States.

In general, the calcium-channel–blocking drugs may decrease the frequency of attacks but have little effect on their severity. It may take weeks to months before an effect is noted, which reduces patient compliance. The adverse effects of these drugs are listed in Table 2. Their vasodilatory action sometimes causes severe headache that is indistinguishable from migraine.

The rationale for the use of calcium-channel blockers to prevent migraine remains to be determined. Calcium regulates vascular smooth-muscle contraction, neurotransmitter release, and neuronal receptor function. Calcium-channel blockade may prevent vasoconstriction and 5-HT release, alter slow potential shifts in the central nervous system, and prevent spreading depression, all of which have been proposed as mechanisms of migraine.[98]

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs have been used for preventive therapy in satisfactorily controlled trials, although some early studies were flawed.[85,89] The most effective such drugs are listed in Table 2.[86-88,90,99] Tolfenamic acid and naproxen were effective in double-blind, placebo-controlled, crossover trials.[88] In the trial of naproxen, up to 52 percent of the patients receiving the drug had no severe headaches, as compared with 19 percent of those given placebo. The severity and duration of headaches, the frequency of nausea and vomiting, and the use of analgesic medication were all reduced in the treatment group. Naproxen was also effective in patients with menstrually related migraine, a condition that is refractory to most therapeutic regimens.[99] Aspirin is also effective in preventing migraine.[90] The adverse effects of nonsteroidal antiinflammatory drugs are listed in Table 2. Prolonged prophylaxis with these drugs should be avoided because of the possibility of gastrointestinal ulceration and bleeding. The relative effectiveness of the various classes of nonsteroidal antiinflammatory drugs has not been studied, but it is reasonable to switch to another class if the first has proved ineffective.

The mechanisms through which nonsteroidal antiinflammatory drugs prevent migraine remain to be determined. They may act by inhibiting prostaglandin synthesis and the initiation of neurogenic inflammation in the trigeminovascular system.[42] There is no association between the degree of platelet inhibition and prophylactic efficacy.[88] Nonsteroidal antiinflammatory drugs may also influence central 5-HT neurotransmission.[44]

Miscellaneous Drugs

Valproic acid was first introduced as preventive therapy for migraine in an open study of 18 patients, 17 of whom reported a benefit from the drug.[91] In a small clinical trial, valproate sodium (800 mg daily) was only moderately effective in preventing migraine and reducing the frequency, severity, and duration of severe attack, as compared with placebo.[92] The side effects of valproic acid are listed in Table 2. An increased incidence of neural-tube defects in infants born to mothers taking valproate limits its use in women of childbearing age. The mechanism of action of valproic acid is not known, but its use is based on the hypothesis that it inhibits the central neuronal hyperexcitability associated with migraine[100] — a relation that also remains to be determined.

Several drugs used to prevent migraine in the past have not been studied adequately and therefore have no place in management now. These include reserpine, trazodone, clonidine, lithium carbonate, dipyridamole, antihistamines, phenytoin, and carbamazepine.

Hormonal Therapy

Menstrual migraine, defined as an attack occurring in association with menses, is frequently refractory to treatment. Women with menstrual migraine may benefit from preventive treatment — for example, propranolol or amitriptyline — limited to the time of their menses or, if they are already receiving prophylactic treatment, from an increased dose at this time. The use of percutaneous estradiol gel, applied just before

and throughout menses, has reduced the frequency of headache in controlled trials.[101,102] Women already taking an oral contraceptive who continue taking it throughout the menstrual cycle may also have fewer attacks.[103]

For women already taking estrogen who have frequent migraine attacks, it may be beneficial either to stop or to increase the hormones.[103] Danazol, an androgen derivative that inhibits pituitary–ovarian function; tamoxifen, an antiestrogen; and bromocriptine, a dopamine-receptor agonist and an inhibitor of prolactin release, have all been reported effective in preventing migraine attacks.[104-106] Since none of these drugs have been studied in clinical trials, however, they cannot be recommended for general use.

The ways in which ovarian hormones influence migraine remain to be determined, but an abrupt decrease in serum estrogen concentrations before the onset of an attack appears to be a critical factor.[107] The low-dose estrogen formulations now used as oral contraceptives are associated with a haphazard occurrence of attacks during the cycle, probably because of fluctuating serum estrogen concentrations. Treatment strategies are therefore aimed at preventing either a decrease or a substantial fluctuation in serum estrogen levels.

Conclusion

Many drugs of varied action have been used in the treatment and prevention of migraine attacks, largely because the cause (or causes) and pathophysiology of the disorder are not known. Nevertheless, there has been progress. For example, sumatriptan was developed specifically as an antimigraine drug on the assumption that 5-HT_1 receptors on the cranial vasculature play a critical part in the mechanisms of a migraine attack. The drug clearly works, suggesting that even more specific 5-HT–receptor agonists can be developed. An improved knowledge of the mechanisms of an attack should also help clarify the pharmacologic properties required by any new drugs developed to be more specifically preventive.

References

1. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8:Suppl 7:1-96.
2. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 1981;9:344-52.
3. Barkley GL, Tepley N, Simkins RT, Moran JE, Welch KMA. Neuromagnetic fields in migraine: preliminary findings. Cephalalgia 1990;10:171-6.
4. Leao AAP. Spreading depression of activity in cerebral cortex. J Neurophysiol 1944;7:359-90.
5. Skyhøj-Olsen T, Friberg L, Lassen NA. Ischemia may be the primary cause of the neurologic deficits in classic migraine. Arch Neurol 1987;44:156-61.
6. Moskowitz MA. The neurobiology of vascular head pain. Ann Neurol 1984;16:157-68.
7. Welch KMA. Migraine: a biobehavioral disorder. Arch Neurol 1987;44:323-7.
8. Gauthier J, Bois R, Allaire D, Drolet M. Evaluation of skin temperature biofeedback training at two different sites for migraine. J Behav Med 1981;4:407-19.
9. International Headache Society Committee on Clinical Trials in Migraine. Guidelines for controlled trials of drugs in migraine: first edition. Cephalalgia 1991;11:1-12.
10. Tfelt-Hansen P, Olesen J. Effervescent metoclopramide and aspirin (Migravess) versus effervescent aspirin or placebo for migraine attacks: a double-blind study. Cephalalgia 1984;4:107-11.
11. Peatfield RC, Petty RG, Rose FC. Double blind comparison of mefenamic acid and acetaminophen (paracetamol) in migraine. Cephalalgia 1983;3:129-34.
12. Hakkarainen H, Gustafsson B, Stockman O. A comparative trial of ergotamine tartrate, acetysalicylic acid and a dextropropoxyphene compound in acute migraine attacks. Headache 1978;18:35-9.
13. Somerville BW. Treatment of migraine attacks with an analgesic combination (Mersyndol). Med J Aust 1976;1:865-6.
14. Hakkarainen H, Quiding H, Stockman O. Mild analgesics as an alternative to ergotamine in migraine: a comparative trial with acetylsalicylic acid, ergotamine tartrate, and dextropropoxyphene compound. J Clin Pharmacol 1989;20:590-5.
15. Johnson ES, Ratcliffe DM, Wilkinson M. Naproxen sodium in the treatment of migraine. Cephalalgia 1985;5:5-10.
16. Pradalier A, Rancurel G, Dordain S, Verdure L, Rascol A, Dry J. Acute migraine attack therapy: comparison of naproxen sodium and an ergotamine tartrate compound. Cephalalgia 1985;5:107-13.
17. Nestvold K, Kloster R, Partinen M, Sulkava R. Treatment of acute migraine attack: naproxen and placebo compared. Cephalalgia 1985;5:115-9.
18. Larsen BH, Christiansen LV, Andersen B, Oleson J. Randomized double-blind comparison of tolfenamic acid and paracetamol in migraine. Acta Neurol Scand 1990;81:464-7.
19. Carasso RL, Peled O, Yehuda S. Flufenamic acid in prostaglandin migraine. Int J Neurosci 1985;27:67-71.
20. Awidi AS. Efficacy of flurbiprofen in the treatment of acute migraine attacks: a double-blind cross-over study. Curr Ther Res 1982;32:492-7.
21. Karachalios GN, Fotiadou A, Chrisikos N, Karabetsos A, Kehagioglou K. Treatment of acute migraine attack with diclofenac sodium: a double-blind study. Headache 1992;32:98-100.
22. Kloster R, Nestvold K, Vilming ST. A double-blind study of ibuprofen versus placebo in the treatment of acute migraine attacks. Cephalalgia 1992;12:169-71.
23. Klapper JA, Stanton JS. Ketorolac versus DHE and metoclopramide in the treatment of migraine headaches. Headache 1991;31:523-4.
24. Selby G, Lance JW. Observations on 500 cases of migraine and allied vascular headache. J Neurol Neurosurg Psychiatry 1960;23:23-32.
25. Schmidt R, Fanchamps A. Effect of caffeine on intestinal absorption of ergotamine in man. Eur J Clin Pharmacol 1974;7:213-6.
26. Hakkarainen H, Allonen H. Ergotamine vs. metoclopramide vs. their combination in acute migraine attacks. Headache 1982;22:10-2.
27. Callaham M, Raskin N. A controlled study of dihydroergotamine in the treatment of acute migraine headache. Headache 1986;26:168-71.
28. Saadah HA. Abortive headache therapy in the office with intravenous dihydroergotamine in the treatment of acute migraine headache. Headache 1992;32:143-6.
29. Belgrade MJ, Ling LJ, Schleevogt MB, Ettinger MG, Ruiz E. Comparison of single-dose meperidine, butorphanol, and dihydroergotamine in the treatment of vascular headache. Neurology 1989;39:590-2.
30. Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. N Engl J Med 1991;325:316-21.
31. Sumatriptan Auto-Injector Study Group. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. Eur Neurol 1991;31:323-31.
32. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H Jr. Treatment of acute migraine with subcutaneous sumatriptan. JAMA 1991;265:2831-5.
33. Oral Sumatriptan International Multiple-Dose Study Group. Evaluation of a multiple-dose regimen of oral sumatriptan for the acute treatment of migraine. Eur Neurol 1991;31:306-13.
34. Anderson BA. Optimizing the dosage regimen for oral sumatriptan — clinical results. In: Clifford-Rose F, ed. New advances in headache research. Vol. 3. London: Smith Gordon (in press).
35. Multinational Oral Sumatriptan and Cafergot Comparative Study Group. A randomized, double-blind comparison of sumatriptan and Cafergot in the acute treatment of migraine. Eur Neurol 1991;31:314-22.
36. Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group. A study to compare oral sumatriptan with oral aspirin plus oral metoclopramide in the acute treatment of migraine. Eur Neurol 1992;32:177-84.
37. Tek DS, McClellan DS, Olshaker JS, Allen CL, Arthur DC. A prospective, double-blind study of metoclopramide hydrochloride for the control of migraine in the emergency department. Ann Emerg Med 1990;19:1083-7.
38. Lane PL, McLellan BA, Baggoley CJ. Comparative efficacy of chlorpromazine and meperidine with dimenhydrinate in migraine headache. Ann Emerg Med 1989;18:360-5.
39. Jones S, Sklar D, Dougherty J, White W. Randomized double-blind trial of intravenous prochlorperazine for the treatment of acute headache. JAMA 1989;261:1174-6.

40. Rapoport A, Weeks R, Sheftell F, et al. Analgesic rebound headache: theoretical and practical implications. Cephalalgia 1985;5:Suppl 3:448-9.
41. Noda S, Umezaki H, Fukuda Y. Response of common migraine and cluster headache attacks to intravenous injection of aspirin. Neurol Med 1984;21: 333-4.
42. Buzzi MG, Sakas DE, Moskowitz MA. Indomethacin and acetylsalicylic acid block neurogenic plasma protein extravasation in rat dura mater. Eur J Pharmacol 1989;65:251-8.
43. Bennett A. Prostaglandins: their release, biological effects and relationships to pain and inflammation. Cephalalgia 1986;6:Suppl 4:17-20.
44. Pradalier A, Vincent D. Migraine et anti-inflammatoires non-steroidiens. Pathol Biol (Paris) 1992;40:397-405.
45. Tansey MJB. The long term safety of sumatriptan. In: Clifford-Rose F, ed. New advances in headache research. Vol. 3. London: Smith Gordon (in press).
46. Dechant KL, Clissold SP. Sumatriptan: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the acute treatment of migraine and cluster headache. Drugs 1992;43:776-98.
47. Stricker BHC. Coronary vasospasm and sumatriptan. BMJ 1992;305:118.
48. Abrahamsen B, Christiansen BD. Angina pectoris after sumatriptan (Imigran). Ugeskr Laeger 1992;154:3602-3.
49. Curtin T, Brooks AP, Roberts JA. Cardiorespiratory distress after sumatriptan given by injection. BMJ 1992;305:713-4.
50. Willett F, Curzen N, Adams J, Armitage M. Coronary vasospasm induced by subcutaneous sumatriptan. BMJ 1992;304:1415.
51. Ottervanger JP, Paalman HJA, Boxma GL, Stricker BHC. Transmural myocardial infarction after sumatriptan. Lancet 1993;341:861-2.
52. Chester AH, Martin GR, Bodelsson M, et al. 5-Hydroxytryptamine receptor profile in healthy and diseased human epicardial coronary arteries. Cardiovasc Res 1990;24:932-7.
53. MacIntyre PD, Bhargava B, Hogg KJ, Gemmill JD, Hillis WS. Effect of subcutaneous sumatriptan, a selective $5HT_1$, agonist, on the systemic, pulmonary, and coronary circulation. Circulation 1993;87:401-5.
54. Lloyd DK, Pilgrim AJ, Simmons VE. Coronary vasospasm and sumatriptan. BMJ 1992;305:310-1.
55. Saxena PR, Ferrari MD. From serotonin receptor classification to the antimigraine drug sumatriptan. Cephalalgia 1992;2:187-96.
56. Moskowitz MA, Buzzi MG. Neuroeffector functions of sensory fibers: implications for headache mechanisms and drug actions. J Neurol 1991;238:Suppl 1:S18-S22.
57. Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. Ann Neurol 1988;23:193-6.
58. Goadsby PJ, Edvinsson L. Sumatriptan reverses the changes in calcitonin gene-related peptide seen in the headache phase of migraine. Cephalalgia 1991;11:Suppl 11:3-4.
59. Spierings ELH, Saxena PR. Antimigraine drugs and cranial arteriovenous shunting in the cat. Neurology 1980;30:696-701.
60. Bell R, Montoya D, Shuaib A, Lee MA. A comparative trial of three agents in the treatment of acute migraine headache. Ann Emerg Med 1990;19:1079-82.
61. Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. Neurology 1986;36:995-7.
62. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci 1984;7:309-38.
63. Lance JW, Curran DA, Anthony M. Investigations into the mechanism and treatment of chronic headache. Med J Aust 1965;2:909-14.
64. Drummond PD. Effectiveness of methysergide in relation to clinical features of migraine. Headache 1985;25:145-6.
65. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. Arch Neurol 1979;36:695-9.
66. Couch JR, Ziegler DK, Hassanein RS. Evaluation of the relationship between migraine headache and depression. Headache 1975;15:41-50.
67. Anthony M, Lance JW. Monoamine oxidase inhibition in the treatment of migraine. Arch Neurol 1969;21:263-8.
68. Weber RB, Reinmuth OM. The treatment of migraine with propranolol. Neurology 1972;22:366-9.
69. Wideroe TE, Vigander T. Propranolol in the treatment of migraine. BMJ 1974;2:699-701.
70. Kuritzky A, Hering R. Prophylactic treatment of migraine with long acting propranolol — a comparison with placebo. Cephalalgia 1987;7:Suppl 6:457-8. abstract.
71. Kangasniemi P, Andersen AR, Andersson PG, et al. Classic migraine: effective prophylaxis with metoprolol. Cephalalgia 1987;7:Suppl 6:464. abstract.
72. Stensrud P, Sjaastad O. Comparative trial of Tenormin (atenolol) and Inderal (propranolol) in migraine. Headache 1980;20:204-7.
73. Johansson V. Atenolol in migraine prophylaxis: a double-blind crossover multicenter study. Headache 1987;27:372-4.
74. Hakkarainen H, Kangasniemi P. Timolol maleate in the prophylactic treatment of classic and common migraine. In: Proceedings of the Timolol Intercontinental Symposium, Stockholm, October 27–28, 1981. New York: Biomedical Information Corp., 1982:433-44.
75. Ryan RE Sr, Ryan RE Jr, Sudilovsky A. Nadolol: its use in the prophylactic treatment of migraine. Headache 1983;23:26-31.
76. Albers GW, Simon LT, Hamik A, Peroutka SJ. Nifedipine versus propranolol for the initial prophylaxis in migraine. Headache 1989;29:215-8.
77. McArthur JC, Marek K, Pestronk A, McArthur J, Peroutka SJ. Nifedipine in the prophylaxis of classic migraine: a crossover, double-masked, placebo-controlled study of headache frequency and side effects. Neurology 1989;39:284-6.
78. Gelmers HJ. Nimodipine, a new calcium antagonist, in the prophylactic treatment of migraine. Headache 1983;23:106-9.
79. Havanka-Kanniainen H, Hokkanen E, Myllyla VV. Efficacy of nimodipine in the prophylaxis of migraine. Cephalalgia 1985;5:39-43.
80. Meyer JS, Hardenberg J. Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headaches. Headache 1983;23:266-77.
81. Stewart DJ, Gelston A, Hakim A. Effect of prophylactic administration of nimodipine in patients with migraine. Headache 1988;28:260-2.
82. Solomon GD, Steel JG, Spaccavento LJ. Verapamil prophylaxis of migraine: a double-blind, placebo-controlled study. JAMA 1983;250: 2500-2.
83. Markley HG, Cheronis JCD, Piepho RW. Verapamil in prophylactic therapy of migraine. Neurology 1984;34:973-6.
84. Markley HG. Verapamil and migraine prophylaxis: mechanisms and efficacy. Am J Med 1991;90:Suppl 5A:5A-48S–5A-53S.
85. Stensrud P, Sjaastad O. Clinical trial of a new anti-bradykinin, anti-inflammatory drug, ketoprofen (19.583 r.p.) in migraine prophylaxis. Headache 1974;14:96-100.
86. Mikkelsen BM, Falk JV. Prophylactic treatment of migraine and tolfenamic acid: a comparative double-blind crossover study between tolfenamic acid and placebo. Acta Neurol Scand 1982;66:105-11.
87. Johnson RH, Hornabrook RW, Lambie DG. Comparison of mefenamic acid and propranolol with placebo in migraine prophylaxis. Acta Neurol Scand 1986;73:490-2.
88. Welch KMA, Ellis DJ, Keenan PA. Successful migraine prophylaxis with naproxen sodium. Neurology 1985;35:1304-10.
89. Masel BE, Chesson AL, Alperin JB, Levin HS, Peters BH. Clinical trial of platelet inhibition, using aspirin and dipyridamole in migraine prophylaxis. Neurology 1978;28:371. abstract.
90. Buring JE, Peto R, Hennekens CH. Low-dose aspirin for migraine prophylaxis. JAMA 1990;264:1711-3.
91. Sorensen KV. Valproate: a new drug in migraine prophylaxis. Acta Neurol Scand 1988;78:346-8.
92. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia 1992;12:81-4.
93. Peroutka SJ. Developments in 5-hydroxytryptamine receptor pharmacology in migraine. Neurol Clin 1990;8:829-39.
94. Mylecharane EJ. $5\text{-}HT_2$ receptor antagonists and migraine therapy. J Neurol 1991;238:Suppl 1:S45-S52.
95. Shanks RG. Mechanisms of action of beta-adrenoceptor antagonists in migraine. In: Carroll JD, Pfaffenrath V, Sjaastad O, eds. Migraine and beta-blockade. Mölndal, Sweden: A.B. Hässle, 1985:45-54.
96. Schoenen J, Timsit-Berthier M, Timsit M. Correlations between contingent negative variation and plasma levels of catecholamines in headache patients. Cephalalgia 1985;5:Suppl 3:480. abstract.
97. Schoenen J, Maertens de Hoordhout A, Timsit-Berthier M, Timsit M. Contingent negative variation and efficacy of beta-blocking agents in migraine. Cephalalgia 1986;6:229-33.
98. Greenberg DA. Calcium channel antagonists and the treatment of migraine. Clin Neuropharmacol 1986;9:311-28.
99. Sargent J, Solbach P, Damasio H, et al. A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. Headache 1985;25:320-4.
100. Welch KMA, D'Andrea G, Tepley N, Barkley G, Ramadan NM. The concept of migraine as a state of central neuronal hyperexcitability. Neurol Clin 1990;8:817-28.
101. de Lignières B, Vincens M, Mauvais-Jarvis P, Mas JL, Touboul PJ, Bousser MG. Prevention of menstrual migraine by percutaneous oestradiol. BMJ 1986;293:1540.
102. Dennerstein L, Morse C, Burrows G, Oats J, Brown J, Smith M. Menstrual migraine: a double-blind trial of percutaneous estradiol. Gynecol Endocrinol 1988;2:113-20.
103. Welch KMA, Darnley D, Simkins RT. The role of estrogen in migraine: a review and hypothesis. Cephalalgia 1984;4:227-36.
104. Sarno AP Jr, Miller EJ Jr, Lundblad EG. Premenstrual syndrome: beneficial effects of periodic, low-dose danazol. Obstet Gynecol 1987;70:33-6.
105. Powles TJ. Prevention of migrainous headaches by tamoxifen. Lancet 1986;2:1344.
106. Andersen AN, Larsen JF, Steenstrup OR, Svendstrup B, Nielsen J. Effect of bromocriptine on the premenstrual syndrome: a double-blind clinical trial. Br J Obstet Gynaecol 1977;84:370-4.
107. Somerville BW. Estrogen-withdrawal migraine. I. Duration of exposure required and attempted prophylaxis by premenstrual estrogen administration. Neurology 1975;25:239-44.